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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/524,060 | 02/08/2005 | Zhiming Suo | US 1421/05 (VA) | 4405 |

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| EXAMINER | |
|---|---|
| WANG, CHANG YU | |
| **ART UNIT** | **PAPER NUMBER** |
| 1649 | |

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/524,060 | SUO ET AL. | |
| | Examiner | Art Unit | |
| | Chang-Yu Wang | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *14-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *February 08, 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. Claims 1-33 are pending. Claims 3, 5, 6, 8, 14-33 are withdrawn from consideration as being drawn to non-elected inventions and species. Claims 1, 2, 4, 7, 9-13 are under examination in this office action.

### *Election/Restrictions*

2. Applicant's election of Group II, the normal distribution of GRK in a prodromal stage of Alzheimer's disease for the species of the disruption and soluble beta-amyloid for the species of peptide in the reply filed on October 11, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 3, 5, 6, 8, 14-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species and inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 11, 2005.

***Priority***

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The priority for this instant application is August 13, 2002.

***Claim Objections***

5. Claim 4 is objected to as encompassing non-elected subject matter.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4, 7, and 9-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a disruption in normal cellular distribution of a G-protein receptor kinase 2/5 (GRK2/5) in association with a transgenic model with early onset of Alzheimer's disease (AD), CRND8 mice, does not reasonably provide enablement for disruption of all forms of GRK distribution and also for detecting all the Alzheimer's pathogenesis as broadly claimed. In addition, while being enabling for detecting the disruption in normal distribution of GRK2/5, does not reasonably provide enablement for detecting the pathogenesis of AD by using soluble β-amyloid peptides in a diagnostic method. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

9. The claims are drawn to a method of detecting Alzheimer's pathogenesis comprising detecting a disruption in normal cellular distribution of a GRK. The instant specification describes that the cellular distribution of GRK2/5 changes in the brains of the AD animal model, CRND8 mice. The specification also teaches that the distribution of GRK2/5 affects the function of G-protein couple receptor (GPCR) in desensitization

and internalization (see p. 4-5, in the specification). There are a lot different members in the family of GPCR in different biological systems, for example, the receptors in response to neurotransmitters, hormones, chemokines, and many other molecules (see p3, paragraph [006]). However, the specification fails to teach how GRK is associated with GPCR in contribution to the pathogenesis of AD or how GRK is a contributory factor for AD pathogenesis. In addition, as the instant specification pointed out that "In AD brains, significant membrane alterations (Reference 22), aberrant phosphoinositide metabolism (Reference 5), disrupted calcium homeostasis (Reference 7) and disorganized cytoskeleton proteins (Reference 23) could all influence the subcellular distribution of GRKS."(see p. 5, lines 1-20, in the specification), suggesting the change of the disritibution of GRK can be derived from different causes and may also lead to other different diseases. There are many possible mechanisms regulating the subcellular distribution of GRK. The specification has not disclosed how the change of distribution can be a determining factor for detecting the pathogenesis of AD. In addition, Applicant fails to disclose or establish that the disruption in normal distribution of GRK2/5 induced by exogenous addition of soluble β-amyloid peptides in vitro can be used as a method of detecting the pathogenesis of AD at prodromal stage, i.e. how can Applicant distinguish the distribution change of GRK2/5 is due to the effects of exogenous addition of soluble β-amyloid or the condition of AD if β-amyloid is the sole contributory factor for AD pathogenesis. The instant specification fails to teach the detailed guidance regarding the detecting the distribution of the GRK can be a method of detecting the pathogenesis of Alzheimer's disease.

10. The prior art has disclosed that many potential mechanisms can be contributed to the pathogenesis of AD, for example, the accumulation of β-amyloid peptides (Hardy et al. Science 2002. 297: 353-356). The β-amyloid deposition is accumulated by neurotoxic β-amyloid peptides, which are derived from the β-amyloid precursor protein (APP). There are many possible mechanisms underlying the accumulation of β-amyloid peptides. One of the possibilities could be due to the mutation of APP because the β-amyloid peptides are derived from endoproteolysis of APP by β and γ-secretases (p. 353, the second paragraph). Another possibility, it could be due to the mutation in presenilin (PS) proteins. It has been shown that the mutation in PS1 and PS2 results in enhancing the processing of APP (p. 353, the third paragraph). Further, it could also be apolipoprotein E (apoE). It has been shown there is a reduction of β-amyloid deposition in APP transgenic mice crossed with the apolipoprotein E (apoE)-deficient mice, suggesting that apoE plays a role in β-amyloid processing and is a contributory factor for the pathogenesis of AD (see p. 353, the Recent Progress Supports the Amyloid Hypothesis). The instant specification has not disclosed any detailed information being enabled for detecting the pathogenesis of AD as broadly claimed. The specification fails to disclose how the distribution of GRK contributes to the pathogenesis of AD. In addition, Applicant fails to disclose whether the change of GRK distribution is a cause or outcome of AD, which is involved in more complex molecular mechanisms. Neither the art nor the instant application has established the role of GRK in the pathogenesis of AD. The specification does not provide enough guidance for detecting the pathogenesis of AD by solely detecting the distribution of GRK. Since the pathogenesis of AD is still

not clear, it would require more undue experiments while a person of skill in the art at the time uses the invention. In addition, it would require more research to elucidate the detailed information on the pathogenesis of AD and the role of GRK in β-amyloid accumulation first before we can conclude whether detecting the GRK distribution is able to detect the pathogenesis of AD.

***Conclusion***

NO CLAIM IS ALLOWED.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

12. Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30

AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
October 28, 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER